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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,452	10/19/2005	Fabio Giannessi	4865-8	6827

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EXAMINER	
THOMAS, TIMOTHY P	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
10/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,452	GIANNESSI ET AL.	
	Examiner	Art Unit	
	Timothy P. Thomas	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-16* is/are pending in the application.

4a) Of the above claim(s) *3-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 9-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/20/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1 and 9-16 in the reply filed on 9/6/2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 3-8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 9/6/2007.

Status of Claims

3. Acknowledgement is made of the amendment to the claims, filed with the response of 9/6/2007. Claim 2 is canceled. Claims 1 and 9-16 are examined on the basis of the merits.

4. It is noted that claims 3-6 have been amended from "use" claims to claims that contain subject matter drawn to a method of treating type 2 diabetes, and are therefore rejoined to the non-elected Group III. Non-elected Group II now contains no claims.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 10-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. The terms "subpharmacological", "subpharmaceutical", and "pharmacological" in claims 10-13 are relative terms which render the claims indefinite. The terms "subpharmacological", "subpharmaceutical", and "pharmacological" are not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

It is not clear where the line falls between "pharmacological" doses and "subpharmacological" or "subpharmaceutical" doses, or whether the terms overlap. There are some of ordinary skill in the art that would interpret "pharmacological" in respect to individual drug doses that would be clinically prescribed for a patient; however, others might consider doses as small as a single molecule of an active compound that potentially interacts with some enzyme or other active site as a "pharmacological" dose. Another issue is whether or not these terms are applied differently to different individuals. Dagogo-Jack ("Pathophysiology of Type 2 Diabetes and Modes of Action of Terapeutic Interventions"; Arch. Intern. Med.; 1997; 157:1802-1817; IDS reference) teaches that dosing with metformin starts at a lower dose (500 or 850 mg) and is increased every 1-2 weeks until an optimum glycaemic effect is achieved or a maximal dose is reached (p. 1808, "Metformin" section). It is clear that an optimal effect, corresponding to a "pharmacological" dose varies with each individual.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1 and 9-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Giannessi, et al. (1999; WO 99/59957 A1; IDS reference), or Giannessi (1999) in

view of Giannessi, et al. (2003; "Discovery of a Long-Chain Carbamoyl Aminocarnitine Derivative, a Reversible Carnitine Palmitolytransferase inhibitor with Antiketotic and Antidiabetic Activity"; J. Med. Chem.; 46: 303-309; published online 12/17/2002; IDS reference) and Dagogo-Jack ("Pathophysiology of Type 2 Diabetes and Modes of Action of Terapeutic Interventions"; Arch. Intern. Med.; 1997; 157:1802-1817; IDS reference).

Giannessi (1999) teaches formula (I) compounds that are useful in treating pathologies such as hyperglycaemia and diabetes (abstract; p. 13, lines 13-15); the compound specie R-4-trimethylammonium-3-(tetradecylcarbamoyl)-aminobutyrate (ST 1326; p. 10, line 7; Example 15); pharmaceutical compositions (p.6, lines 3-5); combination with other active ingredients, such as biguanides (metformin is a biguanide; p. 14, lines 19-20; p. 85, line 11 - p. 86, line 4; p. 91, lines 6-9; claims 18-19); and therapeutic effect can be obtained at dosages between 1-100 mg/kg body weight (corresponds to 70 mg – 7 g for a 70 kg individual; p. 14, line 21-p. 15, line 2); a dosage of 14.5 mg/2ml/kg ST 1326 was administered to 24 hr-starved rats (corresponding to about 1 g for a 70 kg individual; p. 80, lines 7-8); single oral dosage forms are taught (p. 89, line 18. Giannessi (1999) does not teach a combination with metformin by name or doses for metformin, although Gianessi (1999) does teach a combination with biguanides in general, of which metformin is well known. It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the two compounds of instant claim 1, since the artisan would have selected metformin as the biguanide, since this compound has been approved for treatment of diabetes (see Table 3 in

Dagogo-Jack), and since ST 1326 was demonstrated to possess the lowest IC_{50} for inhibition of CPT1 (p. 76, Table 1). It would have been obvious to optimize the combination over different dose ranges for each active compound, including doses within the ranges taught in instant claim 16 and to provide the combination in a single dosage form suitable for therapeutic coverage of the nocturnal fasting period compositions of the instant claims. Upon routine optimization of effective doses of the active ingredients in the combination, the skilled artisan would have utilized doses at or below the lower end of the range taught by Gianessi (1999) and doses at and below normal clinical doses of metformin (the lower doses would fall into a "subpharmaceutical" / "subpharmacological" range; higher doses would fall into the "pharmaceutical" range, depending upon the definitions adopted). The motivation to combine these ingredients would be to provide a more effective combination for patients with type 2 diabetes that do not respond to a single active drug to control glycemic control, including during the fasting period, and the potential of using effective lower doses of one or both active compounds in the combination than for either single drug, with the benefit of reduction of side effects.

Two additional teachings in the prior art provide additional impetus for one skilled in the art to choose the specific active ingredients of the instant claims and a motivation to utilize low pharmacologic and/or subpharmacologic dosages. Giannessi (2003) teaches the compound R-4-trimethylammonium-3-(tetradecylcarbamoyl)-aminobutyrate (compound 17) had one of the best CPT I inhibition activities of compounds tested in pharmacological screening, reduced serum glucose levels in diabetic mice, showed

antiketotic activity in normal fasted rats, and has been selected for development as a potential antiketotic and antidiabetic drug (abstract; p. 307, right 3rd paragraph). Upon reading this paper one of skill in the art would have taken notice that this compound is an excellent drug candidate for diabetes type 2, and possibly type 1. Dagogo-Jack teaches current strategies in treating type 2 diabetes include metformin therapy (the single biguanide oral antidiabetic agent in current use listed in Table 3, used clinically at doses of 1-2.5 g) and suggests one promising strategy is an attack on multiple pathophysiological processes by combining antidiabetic agents with disparate mechanisms of action (abstract); that inhibitors of fatty acid oxidation, which includes agents that inhibit carnitine palmitoyl transferase (CPT1) have shown hypoglycemic, hypolipidemic and insulin-sensitizing effects in patients with dype 2 diabetes ("Inhibitors of Fatty Acid Oxidation" section, p. 1810); metformin has beneficial properties on type 2 diabetes dosages at 500 mg or 850 mg doses are increased weekly until optimal glycemic effect is achieved or a maximum dose is reached ("Metformin", p.1808); known combination therapies include combinations of Metformin with Sulfonylurea or Insulin; dramatic decreases in glucose levels have been observed upon combination over effects of either drug alone (Figure 5); a primary objective of combination therapy taught is to achieve an additive or synergistic effect and thereby improve glycemic control or to neutralize adverse effects of one drug with a second drug to counteract such effects ("Combination Therapies", p. 1811); and other possible two drug combinations including metformin are suggested (p. 1812, middle, 2nd paragraph). One of skill in the art would have taken note that a drug combination with metformin may produce synergistic

effects, and potentially allow lower dosages of either or both drug in combination, which would potentially result in a reduction of side effects and longer effective therapy in type 2 diabetes patients. When considered along with the Giannessi (2003) teaching, it would have been obvious to one of ordinary skill in the art at the time of the invention to prepare the combinations of the instant claims, as outlined in the previous paragraph.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy P. Thomas whose telephone number is (571) 272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TPT/
Timothy P. Thomas
Patent Examiner

Ardin H Marschel 10/13/07
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER